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Understanding Complement-mediated Nervous System aging in Order to Develop Neurodegenerative Therapeutics

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Author's contribution

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Aging is becoming one of the biggest burdens to the developed world, mainly due to it being linked to a variety of diseases from neurodegenerative disorders such as Alzheimer's disease to cancer. It involves the dysregulation of virtually every biological process known, affecting every organ and tissue by distinct mechanisms, the nature of which is only now beginning to be truly understood. This is also true for memory loss, which is considered one of the most typical signs of old age. This is not surprising, given the still limited knowledge regarding how memories and thoughts are stored and utilised by the Central Nervous System (CNS). A potential hint, however, is the recent discovery that the complement system plays a role in synaptic pruning, which is essential for erasing unneeded memories. This is particularly intriguing given that the complement system is a branch of the innate immune system which has been documented as being overactive with aging. This review will thus cover what is currently known about the relationship between the immune system and aging and how the changes in the immune system with age affect the brain in an effort to direct further research. This topic has not been reviewed as a whole, which is why this paper aims to summarise the information on this topic whilst also elaborating on the gaps in research in order to develop potential therapies for neurodegeneration and immunosenescence.

Keywords: Inflammaging; complement; neuronal aging; immunosenescence; synaptic pruning; microglia and astrocytes.

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1. INTRODUCTION

In order to truly understand the role of the complement in neuronal aging, the actual function of the complement must be summarised. The complement is a collection of proteins found in the blood that together aid or "complement" the other branches of the immune system. It does this by stimulating inflammatory responses, opsonising pathogens and even rupturing pathogens. The complement has three pathways by which it can be activated: the classical pathway, the lectin pathway and the alternative pathway. The classical pathway begins with the C1 complex, a multiprotein complex that can be activated through numerous stimuli, with the most well-known being immunoglobulins and the C-reactive protein (CRP). Once activated, the C1r protease cleaves the C1s subunit. This then cleaves C4 into 2 protein fragments C4a and C4b. C4b then binds to C2, which renders it a target for C1s-mediated cleavage. This reaction formsC2a bound to C4b, which will act as a C3 convertase. This means that it will cleave the inactive C3 into the C3a, which acts as a potent inflammatory inducer (anaphylatoxin) and C3b, which then binds to the pathogen membrane for opsonisation. The bound C3b also recruits factor B (FB), which is subsequently cleaved by Factor D to form another complex that can act as a C3 convertase. This begins a positive feedback loop strongly targeting the pathogen for phagocytosis [1]. This then leads to the terminal pathway (TP) occurring when sufficient C3 convertases have been incorporated in the pathogen membrane. This results in the addition of another C3b molecule to the complex, forming a C5 convertase. This hydrolyses C5 forming C5a and C5b with the former stimulating diapedesis and recruitment of immune cells. C5b, however, is added to the membrane together with other complement proteins to form the membrane attack complex (MAC) that forms a membrane pore, which kills the pathogen through osmosis induced lysis [2].

The lectin pathway meanwhile involves either collectins or ficolins, large complexes that recognise specific sugar and acetyl groups that are pathogen specific [3]. When bound to the pathogenic signals, these proteins bind and activate MBL-associated serine protease (MASP) 1 and 2. MASP-1 activates and cleaves MASP-2 at C2 whilst MASP-2 cleaves both C4 and C2 which triggers the complement pathway due to the deposition of the C3 convertase. It is important to note that whilst MASP appears to be a homologue for C1, there are important differences such as in the more flexible stoichiometry of MASP as well as the presence of a third MASP, MASP-3 with distinct functions [4,5].

The alternative pathway meanwhile is distinct in that it does not require a specific signal to activate. Instead, C3 can react with water to form C3 (H_2O), which can bind to FB. This will be cleaved by Factor D (FD) to form an unbound C3 convertase, which will amplify the signal [6]. In order to control this response to actually target pathogens, there are many signals utilised by cells to prevent aberrant activation such as factor H (FH), a protein that binds to glycans produced by self-cells and destabilises the complement pathway by dissociating the C3 convertase on membranes. It also acts as a co-factor for factor I (FI) in order to facilitate degradation of the signal [7].

Whilst it is useful to depict the complement system as a linear pathway with different routes leading to the same response, there are important interactions and complications that influence the complement. For instance, whilst the alternative pathway is treated as a separate pathway, in truth all pathways utilise the alternative pathway to a significant degree to rapidly amplify the complement signal. In fact as little as 10% of C3b molecules incorporated into pathogen membranes are due directly to complement or lectin activation [8,9]. Furthermore the MASP-1/3 mediated cleavage of pro-FB to FB strengthens the alternative pathway, indicating a link between the two pathways [10]. Even in the classical pathway distinct activators can influence the activity of the cascade. Immunoglobulin stimulation initiates the terminal pathway more efficiently than CRP due its tendency to interact with FH to inhibit the formation of the C5 convertase and promote endothelial complement inhibitory factors [11]. Whilst it is easier to visualise the complement activation as a simple step by step process, these alterations must be kept in mind in order to truly appreciate the flexibility of this system and in turn how it changes and adapts in an aging individual.

However, in discussing the complement in relation to the nervous system, certain organ specific differences must be highlighted due to the unique physiology of the CNS. For instance, the complement proteins in the plasma cannot enter the brain due to the Blood Brain Barrier

(BBB) [12]. Instead, complement production is mainly mediated by microglia and astrocytes, which are the main cell types responsible for reacting to damage or infection within the CNS [13,14]. Astrocytes develop from neuronal progenitor stem cells during development, whereas microglial cells develop from a population of macrophages in the yolk sack proceeding to then infiltrate the brain where they reside [15-18]. Both of these cell types have distinct functions, not only in immune response but also in shaping and regulating neural development, both during and after development [reviewed in 19-22]. The CNS is not completely cut off from the rest of the immune system, as plasma circulating immune cells are still able to enter the brain after development, albeit to a small degree [23,24]. The way the extracellular environment affects the entering immune cells and vice versa requires further investigation, especially on how such interactions change during aging. This review will thus revolve around exploring this changing dynamic by both summarising the existing literature and explaining where more research needs to be done to further the field.

Immune aging - the relationship between inflammation and senescence: Before looking at the relationship between the complement and the deterioration of the CNS with aging, it is important to consider the broader changes of the immune system with aging. These changes can be categorised under one of two processes: immunosenescence and inflammaging. Immunosenescence, simply defined, is the observed decrease in immune function with age. Elderly people are known to be at a higher risk of developing harmful infections and more likely to display symptoms, as was made evident during the Sars-COV-2 pandemic [13,15,25,26]. This is mainly due to downregulation of the adaptive immune response for several distinct reasons, such as increased senescence of T-cells and atrophy of the thymus, which leads to reduced production of T-cells [16,19,27,28]. However, in this context, senescence is mainly referring to the ability of these cells to express the senescence associated secretory phenotype (SASP). SASP refers to a collection of inflammatory-inducing cytokines secreted by mainly senescent cells. There is evidence however that the SASP and the inability to proliferate, which is the main feature of senescent cells, may not be mutually exclusive. In fact, it is becoming increasingly likely that the immune cells deemed senescent are exhausted, meaning they can be induced to proliferate provided the right conditions are present [20,29]. This can be shown by the ability of elderly patients to respond to cancer-directed immunotherapy just as well as younger patients when certain immune activators are added to the treatment regimen [23,30]. This distinction is one that is especially important to explore, since being able to reactivate these dormant immune cells might improve the health span of the elderly, whilst also potentially inhibiting the SASP, which strongly contributes to aging as will be discussed later. Such therapy could act as a more targeted form of senolytics, a procedure involving exchanging blood from an elderly person with that of a much younger one, which has shown considerable benefits in certain aged populations [25,31].

However, not all components of the immune system become inactive with age. Certain immune functions have been clearly documented to become overactive as time passes, through a process known as inflammaging. This refers to a subtle but distinct rise in inflammatory signalling without any of the usual markers of inflammation, except for the increased expression of certain cytokines such as Tumour Necrosis Factor α (TNF-α) [26,32]. This increased production of cytokines is likely due to a variety of factors such as mitochondrial dysfunction and the SASP explained previously [27,28,33,34]. Normally such senescent cells are removed via the immune system to avoid such chronic inflammation but with age the proportion of these cells increases, likely due to immunosenescence inhibiting senescent cell clearance [29,35]. This not only links the two processes but it also makes them able to stimulate each other in a positive feedback loop to drive the aging process. This is likely why centenarians have higher levels of anti-inflammatory stimulation [30,36]. Such inflammatory signalling stimulates survival and growth pathways driving the cells towards a cancerous phenotype, at least partially explaining the increased cancer risk found in elderly populations [31,37]. However, whilst this process is associated with the innate immune system, inflammaging is not the same as an overactive innate immune system since some components of the innate immune system are inhibited with age, a phenomenon referred to as innate immune paralysis [32,38]. Neutrophils for instance display reduced chemotactic properties and certain studies report macrophages tending to shift to promoting growth and angiogenesis (referred to as the M2 phenotype) over promoting

the more aggressive and inflammatory associated M1 phenotype, increasing the risk of both infection and cancer [33,39]. This is likely an adaptation of the immune system to the increased amount of senescent and damaged cells in the aged organism to prevent immune-mediated degradation of the remaining healthy tissue at the expense of increased disease risk [34,40].

The complement system is an important modulator of these broad immune changes. This is exemplified in kidney aging, where complement activation leads to expression of inflammatory cytokines as well as collagen promoting inflammaging and collagen synthesis [35,36,41,42]. This makes the complement an effective target for renal disease with significant clinical results [37,43]. It is important to note however, that the kidney is particularly susceptible to complement-mediated damage due to its low expression of complement regulators whilst serving as a prime position for immune complex deposition and complement activation, likely to aid clearing out toxins and pathogens within the nephron [38,44]. That being said, the kidney is an important model for the role the complement system plays in aging with likely more subtle effects in other tissues that require further analysis.

Complement and the brain: As shown the complement system is altered during aging altering its relationships with various biological systems. Evidence suggests that this also extends to the brain, in fact alterations in the complemenet-brain dynamic influence how the morphology of neurological systems change with age. For instance C1q, C3 and C4 levels have been shown to increase in the brain with age [12,45]. Furthermore, astrocyte production of C3 is partly regulated by the transcription factor Nuclear Factor-Kappa b (NF-κB), a transcription factor that produces inflammatory compounds and whose overactivity with age is central to inflammaging [14,17,46,47]. The role of NF-κB could be a core mechanism by which its activation in astrocytes aggravates degeneration, as opposed to NF-κB activation in neurons which has a neuroprotective effect [18,48]. Whilst transcription levels are a useful indicator for complement activity, it is important to note that the transcription rate of complement factors can be a misleading measurement. This is because the complement is produced as inactive precursors and therefore it is the amount of active complement factors that are physiologically relevant rather than the level of inactive protein production. Taking this into consideration, the reduced cognitive decline observed in C3 deficient mice and the significant increase in age-related macular degeneration (AMD) risk in certain polymorphisms of FH, prove that the increased production of complement proteins is in fact resulting in an overactive immune response that is detrimental to the CNS [21,22,49,50].

These changes in the complement are mirrored with dysfunctional microglia. During aging, microglia are less motile and display the signatures associated with senescence [24,45,51,52]. Furthermore, they display decreased wound resolving factors, further aggravating wounds in the CNS as aging progresses [45,52]. The results of these factors can be seen for instance in the retina, where decreased microglial motility but increased complement activation results in microglial-induced activation of retinal pigment epithelium (RPE) cells, giving rise to an inflammatory phenotype [46,53]. Such processes are reminiscent of the inflammaging-immunosenescence axis in the aging immune system. This increase in inflammatory factors and down regulation of other immune responses such as phagocytosis is potentially an adaptation to the increasingly frail organism as a result of aging. By relying more on inflammatory factors that increase cell survival instead of other, perhaps more efficient, responses such as phagocytosis, the increasingly sensitive cells are not at risk of damage by the immune system. This occurs at the expense of an increased risk of both cancer and infections as summarised in Fig. 1 [15,26,34,40,47,54]. However, this dynamic is different in the CNS due to the importance of these immune factors in not just infection but in shaping neuronal function itself. Thus, the shift in the immune system to preserve cellular function results in profound effects in synaptic function that require urgent identification.

Complement and synaptic pruning - a relationship that evolves with age: A rather interesting discovery was that the complement system plays a unique role in the brain and is likely critical to how the complement and the brain interact during aging. As new synapses are formed in response to new information, synapses that are not stimulated for a prolonged period of time degrade through a process known as synaptic pruning [39,48]. The complement

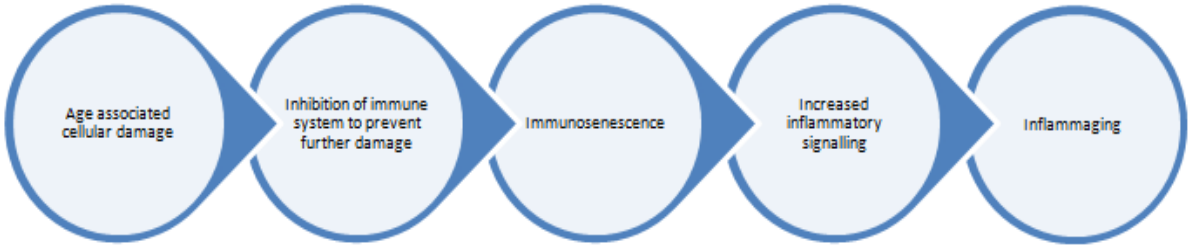

Fig. 1. Diagram displaying a possible mechanism behind the immune system changes as a result of aging and accumulating cellular damage. This also appears to apply to the nervous system which in turn alters the immune modulated process of synaptic pruning. This contributes to age associated cognitive decline, although the significance of this contribution remains to be determined

system aids in the clearance of these synapses as deficiencies in complement proteins such as C1q results in impaired synaptic pruning [43,49]. This can occur through astrocyte-mediated transcription and production of C1q within the neurons themselves that in turn leads to synaptic pruning as has been documented in retinal neurons during post-natal development [40,41,50,51]. This in turn leads to synaptic elimination via microglial cells, the immune cells of the CNS, which engulf the presynaptic termini, degrading the synapse [42,52]. The complete cellular mechanism behind this process and whether it occurs in all neurons or if distinct processes exist depending on the location and developmental stage are currently both unknown. However, the broad inhibition of synaptic pruning associated with complement inhibition suggests that the complement is a part of this process [40,50]. Despite this involvement however, synaptic pruning still occurs following complement inhibition, indicating that the process is not entirely dependent on the complement. Furthermore, other immune factors such as the major histocompatibility complex (MHC) appear to aid in synaptic pruning indicating that the process is intricately regulated by multiple branches of the immune system [44,53].

Altering complement interactions within the brain can also affect neurons indirectly via damage to the BBB. The BBB is a crucial neurological structure consisting of endothelial cells, pericytes and astrocytic end feet. This structure is crucial in serving as a protective barrier to allow the brain to be an immune privileged site whilst also reducing the risk of infections. The endothelial cells that form the BBB contain receptors for both C3a [C3aR] and C5a (C5aR) complement proteins allowing the complement to actually impact BBB functioning [55]. C3aR stimulation for instance leads to an increase in intracellular calcium. This in turn results in stress fibre formation which decreases vascular endothelial-cadherin (VE-cadherin) decreasing BBB integrity [56]. This, in addition to the increased expression of vascular cell adhesion molecules, results in increased lymphocyte infiltration promoting neuroinflammation. This neuroinflammation increases IFN-γ and C3 production in the infiltrating T-cells which in turn promotes NF-kB in astrocytes increasing complement stimulation [14,57,58]. This results in a potential positive feedback loop that could be one of the core mechanisms behind age-associated neurodegeneration. Furthermore, C5a activity stimulates NF-kB in endothelial cells, which upregulates caspase activity. This causes apoptosis to further disrupt the BBB [55]. Due to this complement mediated BBB breakdown, inhibition of these pathways aids in preventing neurological damage. Inhibition of C3aR in endothelial cells specifically, resulted in significant improvements to BBB functioning in aged mice [56]. Additionally C5aR inhibition has also been shown to increase BBB integrity [59]. However there are other complement-BBB interactions that actually increase BBB integrity. For instance, complement component 8 gamma (C8G) is a subunit in the membrane attack complex (MAC) that is capable of inhibiting sphingosine-1-phosphate receptors (S1PR). This interaction prevents the inflammatory effects of S1P thus inhibiting lymphocyte infiltration (70). In short it is clear that the complement can impact neurological functioning without affecting synaptic pruning via the BBB. The nature, implications and modes of action of these mechanisms remains to be fully determined but even with the limited data available it is clear that targeting the complement is a viable means to maintain the BBB, even though there are certain situations where activity of certain complement components should be encouraged to maintain

the BBB. That being said, much more research needs to be done to determine the optimal means to manipulate the complement to conserve BBB integrity.

Complement inhibition as a potential neurodegenerative therapy: The clear upregulation of the complement with age presents an interesting target to treat age-associated cognitive impairments. As mentioned previously, inhibition of C3 managed to reduce the age-associated cognitive decline in mouse models [49,54]. Furthermore, decreased C1q levels inhibit synaptic loss in a model of Alzheimer's disease (AD), although the model utilised is more similar to the forms of AD which are caused by a single genetic mutation rather than that observed in aging [60]. Such discrepancies are important to point out as complement inhibition does not always result in improved synaptic stability. For instance, in models of Parkinson's disease, C1q deficiency had no significant effect on the cognitive decline in the mice tested and in models of Amyotrophic Lateral Sclerosis (ALS) C1q inhibition exacerbated the symptoms [61,62].

This indicates that, whilst complement activation generally increases synaptic pruning, this pathway can be carefully modulated to have different outcomes, depending on the specific signal and the microenvironment the pathway is taking place in. This complexity must be taken into account when next generation therapeutics are designed. Rather than outright inhibit, these should mould the complement to contribute to healthy functioning of the organism. In cancer, various kinds of malignant cells provide a microenvironment that steers the complement to further stimulate tumour growth [63]. For instance, cancer cells express high amounts of complement regulators so that only sub-lytic concentrations of the MAC forms on the membranes, which instead of lysing the cells stimulates growth via activation of phosphatidylinositol 3-kinase (PI3K) [64]. Furthermore, the highly inflammatory compounds produced via complement activation aid in the maintenance of tumour growth and survival [65]. C1q has also been shown to stimulate Wingless and Int-1 (WNT) signalling through C1q binding to Frizzled receptors, which promotes neural survival, BBB integrity and even neurogenesis, with the WNT pathway being considered as a potential treatment target for AD [65,66]. Therefore, a greater understanding for the interactions between the complement and synaptic functioning are required to design therapies that guide the complement to not only inhibit degradation of synapses but also promote neuronal survival and regeneration [67].

Furthermore, it is also important to note the importance of synaptic pruning in neuronal physiology. Removing unnecessary synapses is essential for retaining efficiency within the brain. This is exemplified by the impairment of social behaviour and repetitive action observed in mice upon inhibition of microglial-mediated synaptic pruning [68]. Furthermore, the destabilisation of memories, especially long-term ones, is now being considered a crucial process both for memory retrieval and alteration. However, the mechanisms underlying both processes are still being studied. The complement system could play an integral part in this process, aiding in the destabilisation of synaptic circuits to allow for their modulation or potential elimination [69]. Therefore, a greater understanding of synaptic regulation and utilisation is necessary to ensure that complement targeted therapies manage to revitalise neuronal function as much as possible.

Future Perspective: The role of the complement in neurological aging is still not well characterised with many distinct aspects that require further study. The largest gap in the current knowledge is the neuronal specific functioning of the complement and the cells producing it. Furthermore, how it responds and interacts to signals external to the CNS such as via immune cell infiltration remains to be determined. This then leads potentially to the molecular details underlying the complement's role in synaptic pruning and how it can be modulated in accordance with local signalling. Finally, a greater understanding of the benefits of the complement in the CNS will be essential to preserve or even enhance these interactions whilst inhibiting the deleterious effects of the complement system [70].

2. CONCLUSIONS

The immune system and CNS are considered the 2 most complex systems in the human body. It makes sense that it is their interaction that in turn leads to the most complex disease, aging. The complement system functions as a crucial interaction point between the two systems as it is utilised both to target and kill pathogens as well as modulate synapses and aid in neural development. The crucial role of the complement can however become detrimental as the

organism struggles to maintain homeostasis due to the process of aging resulting in dysregulation and the associated immune deficiencies, diseases and cognitive decline. The actual mechanisms by which complement affects neurological functioning and the variety with which it impacts different processes are still not well understood. That being said, research is beginning to suggest that the complement can be a suitable target, under the right circumstances, to treat age associated neurological decline via its roles in both synaptic pruning and BBB functioning. It is by understanding the exact pathways that activate and are activated by the complement that targeted therapeutics can be developed that can guide this system to behave more like its name suggests, rather than an insult

HIGHLIGHTS

Complement system is an integral component of the innate system with a dynamic context dependent role.

Complement forms part of the innate immune system, parts of which become overactive during aging, a phenomenon known as inflammaging.

Given that the complement stimulates synaptic pruning, it is plausible that complement overactivation results in the cognitive impairment typical of aging.

Transcript levels of complement factors are increased during aging, inhibition of which tends to ameliorate aging associated cognitive decline in mice.

Therefore, the complement modifying therapies could be core to promoting healthy neuronal aging.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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